(12) UK Patent Application (19) GB (11) 2 146 987 A

(43) Application published 1 May 1985

(21) Application No 8423710

(22) Date of filing 19 Sep 1984

(30) Priority data

(31) 5156/83 (32) 22 Sep 1983 (33) CH
8349/83 28 Nov 1983

(51) INT CL⁴
C07D 249/08 A61K 31/41 C07D 233/60

(52) Domestic classification
C2C 1173 1175 1300 1410 1450 215 220 225 226 227 22Y 246 250 252 253 25Y 305 30Y 311 313 31Y 326 338 351 355 35X 360 363 36Y 373 37Y 386 401 402 40Y 463 48Y 502 50Y 551 613 623 625 62Y 652 665 666 697 699 69Y 73Y 770 778 779 77X 77Y 802 80Y AA NR QN UP WK ZA
U1S 1306 2410 C2C

(56) Documents cited
None

(58) Field of search
C2C

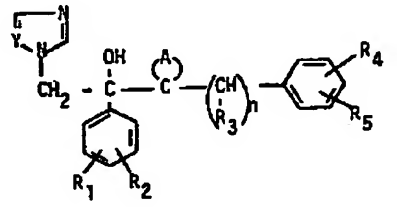
(71) Applicant
Sandoz Ltd. (Switzerland),
35 Lichtstrasse, CH-4002 Basle, Switzerland

(72) Inventor
Helmut Egger

(74) Agent and/or Address for Service
B. A. Yorke & Co.,
98 The Centre, Feltham, Middlesex TW13 4EP

(54) Azole derivatives process for their production compositions containing them and their use

(57) A compound of formula I



I

wherein

R_1 and R_2, independently, are hydrogen, halogen, nitro; or unsubstituted or mono- or poly-halogen substituted lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy or lower alkylthio; or unsubstituted or substituted phenyl or phenoxy,

R_3 is hydrogen or lower alkyl,

R_4 and R_5, independently, are hydrogen or halogen,

Y is CH or N,

A is a C_{2-7}methylene bridge and

n is 0 or 1, in free base form or in the form of an acid addition salt or a physiologically-hydrolysable and -acceptable derivative,

which compounds are indicated for use as chemotherapeutic agents e.g. as *anti-mycotics* and in addition as *fungicides*.

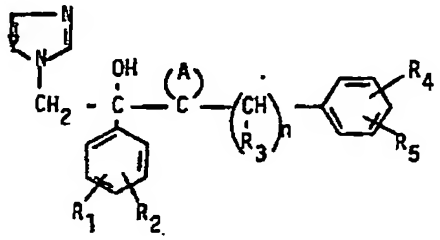
GB 2 146 987 A

SPECIFICATION

Azole derivatives, process for their production compositions containing them and their use

The present invention concerns azole derivatives, a process for their production, pharmaceutical compositions containing them and their use as pharmaceuticals, e.g. as anti-mycotics and as agrochemicals e.g. as fungicides.

In particular the invention concerns compounds of formula I



I

wherein

R_1 and R_2, independently, are hydrogen, halogen, nitro or unsubstituted or mono- or poly-halogen substituted lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy or lower alkylthio or unsubstituted or substituted phenyl or phenoxy,

R_3 is hydrogen or lower alkyl,

R_4 and R_5, independently, are hydrogen or halogen,

Y is CH or N,

A is a C_{2-7} alkylene bridge and

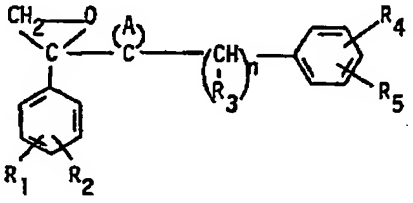
n is 0 or 1,

in free base form or in the form of an acid addition salt or a physiologically-hydrolysable and acceptable derivative.

By the term "physiologically-hydrolysable and -acceptable derivative" is meant e.g. an ester of a compound in accordance with the invention in which the hydroxy moiety is esterified, and which is hydrolysable under physiological conditions to yield in the case of an ester, an acid which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels.

Lower alkyl moieties appearing in or as substituents preferably contain 1 to 5, especially 1 to 3 carbon atoms, lower alkenyl and alkynl preferably 2 to 5 especially 2 or 3. Halogen stands for F, Cl, Br or I. Examples of halogenated groups as R_1 and R_2 are mono-, di- or tri-substituted groups such as CF_3, CH_2Cl, C_2H_5Cl, $CBr{=}CH_2$; $OCHF_2$, SCF_3, $C{\equiv}CBr$, ClC_6H_4, $Cl_2C_6H_3O$. Examples of suitable unsubstituted groups as R_1 and R_2 are H, halogen, CH_3, C_2H_5, $CH{=}CH_2$, $C{\equiv}CH$, OCH_3, SCH_3, C_6H_5, C_6H_5O, NO_2.

The compounds of formula I and their acid addition and physiologically-hydrolysable and -acceptable derivatives may be prepared according to the invention by reacting a compound of formula II



II

with a compound of formula III

III

wherein

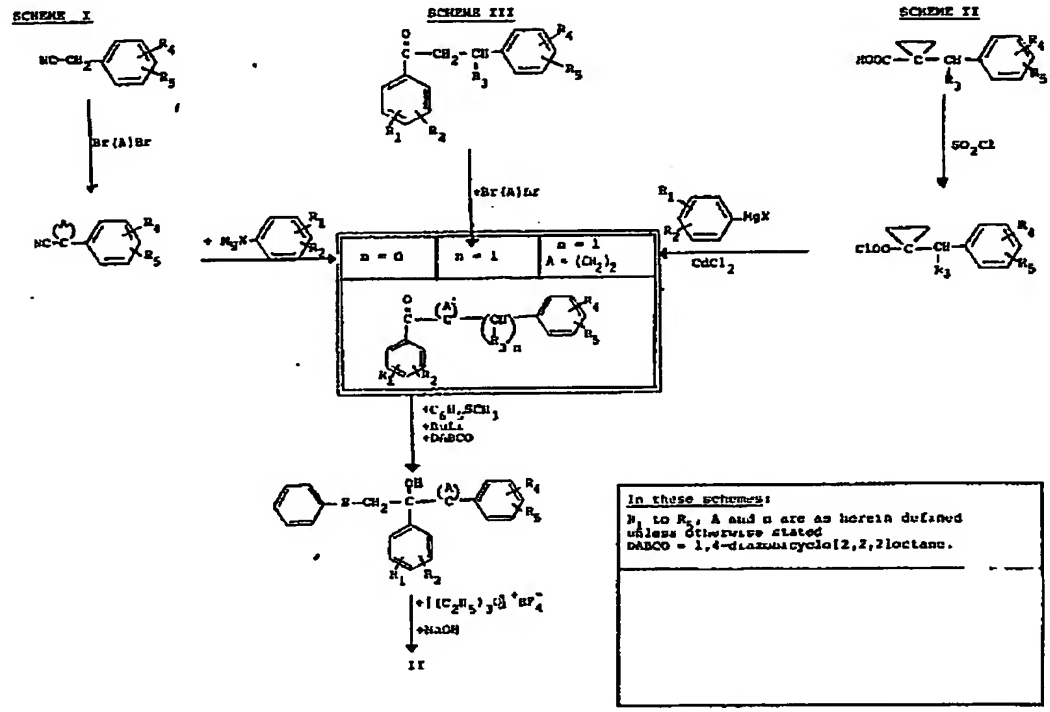
R_1 to R_5, Y, m and n are as defined above

and M is hydrogen, a metal, or a trialkylsilyl group,

and isolating the compound thus obtained in free base form or in the form of an acid addition salt or physiologically-hydrolysable and -acceptable derivative. The reaction may be carried out in conventional manner for example by treating a compound of formula III wherein M is hydrogen dissolved in a solvent inert under the reaction conditions e.g. dimethylsulfoxide, with sodium hydride and then adding the oxirane of formula II preferably dissolved in the same solvent and stirring the mixture at room temperature.

Examples of metals as M are alkali metals such as sodium, trialkylsilyl is for example trimethylsilyl.

The desired end product can be isolated and purified in conventional Manner and recovered in free base form or in the form of an acid addition salt or physiologically-hydrolysable and -acceptable derivative.



Free base forms and other forms such as salt and e.g. ester forms can also be interconverted in conventional manner

The starting materials of formula II are new and can be prepared for example according to the reaction schemes 1, 2 and 3 which are carried out in conventional manner e.g. as described in the examples. The products may be isolated and purified in conventional manner or directly further reacted, as appropriate.

Remaining intermediates are either known or may be prepared analogously to known methods and/or analogously to the examples hereinafter.

The compounds of formula I exhibit chemotherapeutic, in particular local and peroral anti-mycotic activity as indicated *in vitro* on families and species of mycetes e.g. Trichophyton, Aspergillus, Microsporium, Sporothrix and Candida in serial dilution tests and in the germ tube inhibition test (C. albicans) at concentrations of 1.5 to 100 μg/ml and 0.05 μg/ml respectively and *in vivo* in the experimental genital mycosis model in mouse and rat e.g. on peroral administration at between ca. 3 and 25 mg/kg animal body weight.

The compounds are therefore indicated for use as pharmaceuticals particularly an anti-mycotics.

An indicated suitable daily dosage for use as an anti-mycotic is from about 20 to 1500 mg. If desired this may be administered in divided doses 2 to 4 times a day in unit dosage form containing from about 5 to 750 mg of the compound or in sustained release form.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts e.g. as the hydrochloride, hydrogen fumarate or naphthalin-1,5-disulphonate or in the form of a physiologically-hydrolysable and -acceptable derivative preferably an ester. Such forms exhibit the same order of activity as the free base forms.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally other excipients and administered orally, topically, i.v. or parenterally in such forms as tablets, capsules, creams, tinctures or injectable preparations.

Such compositions also form part of the invention.

The invention therefore also concerns a method of combatting infections and diseases caused by mycetes comprising administering to a subject in need of such treatment an effective amount of a compound of formula I in free base form or in the form of a chemotherapeutically acceptable acid addition salt or physiologically-hydrolysable and -acceptable derivative thereof, and such compounds for use as chemotherapeutic agents, in particular as anti-mycotic agents.

The compounds of the invention in free form or in agriculturally acceptable salt or metal complex form are also suitable for combatting phytopathogenic fungi. This fungicidal activity can be demonstrated i.a. in *in vivo* tests against Uromyces appendiculatus (bean rust) on runner beans as well as against other rust fungi (e.g. Hemileia, Puccinia) on coffees, wheat, flax and ornamentals (e.g. pelargonium, snapdragon); and against Erysiphe cichoracearum on cucumber as well as against other powdery mildews (e.g. E. Graminis f. sp. tritici. E. gram. f. sp. hordei, Podosphaera leucotricha, Uncinula recator) on wheat, barley, apple and vines.

Preferred substituent meanings are

R_1 and R_2,		independently, =
		a) hydrogen
		b) halogen especially for Cl or
		c) one hydrogen the other halogen especially F or Cl,
R_3	=	a) hydrogen
		b) alkyl,
R_4 and R_5,		independently, =
		a) hydrogen
		b) halogen especially F or Cl or
		c) one hydrogen the other halogen especially F or Cl,
Y	=	a) N
		b) CH
A	=	a) a C_2, 4 or 6 alkylene bridge
		b) ethylene or butylene
n	=	a) 0
		b) 1.

Free base and acid addition salt forms are preferred.

Especially preferred are combinations of the above mentioned substituent meanings.

A particular compound group is that comprising compounds of formula I wherein

R_1 and R_2, independently, are hydrogen, halogen, nitro or optionally halogenated lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy or lower alkylthio or optionally substituted phenyl or phenoxy,
R_3 is hydrogen or alkyl,
R_4 is hydrogen or halogen,
R_5 is halogen,
Y is CH or N
A is a C_{2-7} alkylene bridge and
n is 0 or 1,

in free base form or in the form of an acid addition salt.

Another compound group is that wherein R_1 and R_2 are hydrogen or halogen, R_3 is hydrogen, R_4 and R_5 are hydrogen or halogen and Y, A and n are as defined above.

Within this group halogen is preferably F or Cl and one each of R_1 and R_2, and R_4 and R_5 is hydrogen. In this case halogen is preferably para-positioned.

A preferred compound is 1-[1-(4-chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-fluorophenyl)cyclopropane in free base form or in the form of an acid addition salt or physiologically-hydrolysable and -acceptable derivative.

The following examples illustrate the invention, tempeatures being in degrees centigrade.

EXAMPLE 1

1-[1(4-Chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1(4-chlorophenyl)cyclopropane

A solution of 1.81 g of 1,2,4-triazole in 20 ml of abs. dimethylsulfoxide is mixed, under argon atmosphere with stirring and ice-cooling, with 0.63 g of sodium hydride (ca. 50% dispersion in mineral oil) and then

allowed to warm up to RT within 1 hour. To this is added a solution of 0.8 g of 2-[l-(4-chlorophenyl)]cyclopropyl-2-(4-chlorophenyl)oxirane in 5 ml of abs. dimethylsulfoxide and stirred for 24 hours at RT. For working-up the reaction mixture is poured into saturated sodium chloride solution and extracted with ethylacetate and the organic phase dried over sodium sulphate and evaporated. The crude product is dissolved in a little dichloromethane and diluted with ether to obtain colourless crystals m.p. 103-106°.

The following compounds may be prepared analogously to Example 1 or as otherwise hereinbefore described.:

Ex.	R_1	R_2	R_3	R_4	R_5	*Y*	*A=(CH₂)ₘ m*	*n*	*physico-chemical characteristics*
2	4-Cl	H	–	H	4-Cl	CH	2	0	mp.194-198°
3	4-Cl	H	–	H	4-Cl	N	4	0	mp. 127-135°
4	4-Cl	H	–	H	4-Cl	CH	4	0	mp. 155-160°
5	4-Cl	H	H	H	4-Cl	N	2	1	mp. 140-150°
6	4-Cl	H	H	H	4-Cl	CH	2	1	mp. 183-185°
7	4-Cl	H	H	H	4-Cl	CH	4	1	mp. 169-172°
8	4-Cl	H	–	H	2-F	N	2	0	mp. 120°
9	4-F	H	–	H	4-F	N	2	0	mp. 103-105°
10	4-Cl	H	–	H	4-F	N	2	0	mp. 125°
11	H	H	–	H	H	N	2	0	mp. 185-187°

The required starting materials may be prepared as follows:

A) 2-[1-(4-Chlorophenyl)]cyclopropyl-2-(4-chlorophenyl)oxirane
(for examples 1 and 2)

a) 1-(4-Chlorophenyl)cyclopropane nitrile

30 g of 4-Chlorobenzylcyanide are dissolved in 300 ml of a mixture of dry tetrahydrofurane and dimethylsulfoxide (1/1) cooled to 10° and reacted with stirring with 79 g of dry pulverised (ball-mill) sodium hydroxide. 37.1 g of 1,2-dibromoethane are added dropwise to this mixture with thorough stirring in such a way that the temperature does not exceed 15°. On completion the mixture is stirred for 45 minutes at RT and then poured into saturated sodium chloride solution and extracted with ethylacetate. The combined ethylacetate phases are washed with NaCl solution, dried over sodium sulphate and concentrated under vacuum. The residue is vacuum destilled, b.p. 92-94°/1.33 Pascal. The product commences to crystalise in the cooler m.p. 42-45°.

b) 1-(4-Chlorobenzoyl)-1-(4-chlorophenyl)cyclopropane

A Grignard solution is prepared in conventional manner from 64.9 g of 4-bromochlorobenzene and 7.5 g of magnesium turnings in abs. ether. To this are added dropwise 17 g of 1-(4-chlorophenyl)cyclopropannitrile and the mixture then refluxed for 2 hours. The reaction mixture is carefully mixed under cooling with half its volume of 6N HCl and refluxed for 3 hrs. to hydrolyse the ketimine formed. Working-up is carried out by dilution with NaCl solution, extraction with ethylacetate, evaporation and chromatography on silica gel 60 (petroleum ether/ether : 10/1). A colourless oil results which according to TLC and NMR is uniform.
NMR ($CDCl_3$): 1.25 and 1.68 (each 2H, m, CH_2); 7.18 (4H, m); 7.25 (2H, m); 7.70 (2H,m).

c) 1-(4-Chlorophenyl)-1-[1-(4-chlorophenyl)-1-hydroxy-2-phenylthio]ethyl-cyclopropane

A solution of 7.46 g of thioanisole and 6.74 g of 1,4-diazabicyclo-[2,2,2]octane ("DABCO") in 40 ml of dry tetrahydrofuran is cooled to 0° and under argon atmosphere slowly mixed with a solution of 3.85 g of n-butyllithium in n-hexane. The mixture is allowed to warm to RT and stirring continued for 40 mins. The mixture is again cooled to 0°, a solution of 7 g of 1-(4-chlorobenzoyl)-1-(4-chlorophenyl)cyclopropane in 40 ml dry tetrahydrofuran added dropwise with stirring and after removal of the cooler stirring continued for 45 mins. Working-up is carried out by pouring in ice-cold NaCl solution, extraction with ethylacetate, evaporation and chromatography on silica gel 60 (toluene/petroleum ether : 1/1). A colourless oil results which according to TLC and NMR is uniform.
NMR ($CDCl_3$): 0.83 and 1.30 (each 2H, m, cyclopropane-CH_2); 3.04 (1H, s, OH); 3.42 and 3.83 (each 1H, AB-q, J = 13, 1Hz, $-SCH_2$); 6.8-7.4 (13H, m, aromatics).

d) 2-[1-4-chlorophenyl) cyclopropyl]-2-(4-chlorophenyl)oxirane

8 g of 1-(4-chlorophenyl)-1-[1-(4-chlorophenyl)-1-hydroxy-2-phenylthio] ethylcyclopropane are dissolved in 30 ml of dry dichloromethane and reacted with 9.1 g of triethyloxonium fluoroborate by stirring at RT for 3 hours. Then an equal volume of 0.5N sodium hydroxide was added and the mixture stirred overnight. Working-up is carried out by separating phases, removal of solvent and the residue chromatographed on silica gel 60 (toluene/petroleum ether : 1/1). A colourless, viscous mass results which according to TLC and NMR is uniform.

NMR ($CDCl_3$): 0.7-1.25 (4H, m, cyclopropane); 2.92 and 3.10 (each 1H, AB-s, J=5.4Hz, $-CH_2O$); 7.0-7.3 (8H, m, aromatics).

B) 2-[1-(4-Fluorophenyl)cyclopropyl]-2-(4-chlorophenyl)oxirane
(for example 10)

a) 1-(4-Chlorobenzoyl)-1-(4-fluorophenyl)cyclopropane

A Grignard solution is prepared in conventional manner from 45.2 g 4-bromochlorobenzene and 6 g of magnesium turnings in abs. ether. Upon completion of the reaction by 1/2 hr. refluxing 6 g of abs. pyridine and then 12.7 g of 1-(4-fluorophenyl)cyclopropannitrile are added dropwise with stirring. The mixture is refluxed for 2 hours, carefully mixed under ice cooling with 250 ml of 6N HCl and refluxed for 3 hours to hydrolyse the ketimine formed. Working-up is carried out by dilution with NaCl solution, extraction with ethylacetate, evaporation and chromatography on silica gel 60 (toluene/petroleum ether : 60-80° 1/1). A colourless oil results which according to TLC and NMR is uniform.
NMR ($CDCl_3$): 1.33 and 1.66 (each 2H, m, cyclopropane); 6.85-7.35 (6H, m, aromatics); 7.60-7.75 (2H, m, aromatics).

b) 1-(4-Fluorophenyl)-1-[1-(4-chlorophenyl)-1-hydroxy-2-phenylthio]ethyl-cyclopropane

Analogously to A). The compound is employed in next step without further purification.

c) 2-[1-(4-Fluorophenyl)cyclopropyl]-2-(4-chlorophenyl)oxirane

Analogously to A).
NMR ($CDCl_3$): 0.6-1.2 (4H, m, cyclopropane); 2.88 (1H, d, J=5,4 Hz) and 3.08 (1H, d, J=5,4 Hz, $-CH_2O$); 6.8-7.3 (8H, m, aromatics).

C) 2-[1-(4-Chlorophenyl)cyclopentyl]-2-(4-chlorophenyl)oxirane
(for Examples 3 and 4)

Analogous to A) or B).

a) 1-(4-Chlorophenyl)cyclopentanenitrile

Colourless oil bp: 116°/1.33 Pascal (purity HPLC 99%).
NMR ($CDCl_3$): 1.8-2.6 (8H, m); 7.3-7.5 (4H, m).

b) 1-(4-Chlorobenzoyl)-1-(4-chlorophenyl)cyclopentane

NMR ($CDCl_3$): 1.6-2.6 (8H, m); 7.15-7.40 and 7.52-7.65 (together 8H, m).

c) 1-(4-Chlorophenyl)-1-[1-(4-chlorophenyl)-1-hydroxy-2-phenylthio]ethyl-cyclopentane

NMR ($CDCl_3$(: 1.2-2.3 (18H, m); 3.22 (1H, s, OH); 3.28 and 3.83 (each 1H, AB-q, J=13Hz); 6.9-7.3 (13H, m).

d) 2-[1-(4-Chlorophenyl)cyclopentyl]-2-(4-chlorophenyl)oxirane

NMR ($CDCl_3$): 1.5-2.05 (8H, m); 2.74 and 3.27 (each 1H, AB-q, J=5Hz); 6.74-6.79 (2H, m); 7.06-7.27 (6H, m).

D) 2-[1-(4-Chlorophenyl)cyclopropyl]-2-(4-chlorobenzyl)oxirane (for Exs. 5 and 6)

a) 1-(4-Chlorobenzoyl)-1-(4-chlorophenyl)cyclopropane

A Grignard solution is prepared in conventional manner from 14.4 g of 4-bromochlorobenzene and 2 g of magnesium turnings in 100 ml of abs. ether. 6.9 g of pulverised cadmium chloride are added and the mixture refluxed for 1 hour. The ether is replaced by 100 ml of dry benzene and a solution of 15 g of 1-(4-chlorobenzyl)cyclopropane-carboxylic acid chloride in 20 ml of benzene is added in one lot at 60. The resulting mixture is refluxed for one hour, poured into ice-cold ammonium chloride solution and extracted with ethylacetate. The organic phase is washed successively with 2N HCl and saturated sodium hydrocarbonate solution, dried over sodium sulphate and evaporated. Chromatography on silica gel 60 (toluene) yields colourless crystals of the title compound m.p. 92.93°.

Steps b) and c) are carried out analogously to A) or B).

b) 1-(4-Chlorophenyl)-1-[1-(4-chlorobenzyl)-1-hydroxy-2-phenylthio]ethyl-cyclopropane

c) 2-[1-(4-Chlorophenyl)cyclopropyl]-2-(4-chlorobenzyl)oxirane

Colourless oil.

E) 2-[1-(4-Chlorophenyl)cyclopentyl]-2-(4-chlorobenzyl)oxirane
(for Example 7)

a) 1-(4-Chlorobenzoyl)-1-(4-chlorobenzyl)cyclopentane

5 g of 4-Chloro-3-(4-chlorophenyl)propiophenone are dissolved in 50 ml of a mixture of dry tetrahydrofuran and dimethylsulphoxide (1/1) cooled to 0° and mixed with stirring with 7 g of pulverised (ball-mill) sodium hydroxide. 3.86 g of 1.4-dibromobutane in 5 ml of dry tetrahydrofuran are added with thorough stirring at 0°.

After removal of the oil-bath the mixture is stirred for a further 40 minutes, then poured into sat. NaCl solution and extracted with ethylacetate. The combined organic phases are washed with sodium chloride dried over sodium sulphate and concentrated under vacuum. The residue is chromatographed on silica gel 60 (toluene/petroleum ether : 4/1). The title compound is isolated from the second main fraction as a colourless oil.
NMR ($CDCl_3$): 1.6-2.4 (8H, m); 3.15 (2H, s); 6.8-7.8 (8H, m).

Steps b) and c) are carried out analogously to A) or B).

b) 1-(4-Chlorophenyl)-1-[1-(4-chlorobenzyl)-1-hydroxy-2-phenylthio]ethyl-cyclopentane
Colourless oil

c) 2-[1-(4-Chlorophenyl)cyclopropyl]-2-(4-chlorobenzyl)oxirane
The oily crude product is reacted without further purification.

F) 2-[1-(4-Chlorophenyl)cyclopropyl]-2-(2-fluorophenyl)oxirane (for Example 8)
Analogously to A) or B).

a) 1-(2-Fluorophenyl)cyclopropanenitrile
bp: 66°/13.33 Pascal
NMR ($CDCl_3$): 1.40 and 1.69 (each 2H, m, cyclopropane); 7.05-7.4 (4H, m, aromatics).

b) 1-(4-Chlorobenzoyl)-1-(2-fluorophenyl)cyclopropane
NMR ($CDCl_3$): 1.35 and 1.80 (each 2H, m, cyclopropane); 6.8-7.6 (8 H, m, aromatics).

c) 1-(2-Fluorophenyl)-1-[1-(4-chlorophenyl)-1-hydroxy-2-phenylthio]ethyl-cyclopropane
NMR($CDCl_3$): 0.50-0.85 (2H, m. cyclopropane); 1.34 (2H, m, cyclopropane); 3.10 (1H, s, −OH); 3.50 and 3.96 (each 1H, dq, J=13.5 Hz and 1.8 Hz, $-SCH_2$); 6.8-7.3(13H, m, aromatics).

d) 2-[1-(4-Chlorophenyl)cyclopropyl]-2-(2-fluorophenyl)oxirane
NMR ($CDCl_3$): 0.55-1.15 (4H, m, cyclopropane); 2.93 (1H, d, J=5.4 Hz); 3.14 (1H, dd, J=5.4 and 2.0 Hz, $-CH_2O$); 6.9-7.2 (8H, m, aromatics).

G) 2-[1-(4-Fluorophenyl)cyclopropyl]-2-(4-fluorophenyl)oxirane (for Example 9)
Analogously to A) or B).

a) 1-(4-Fluorophenyl)cyclopropannitrile
bp: 66°/13.33 Pascal
NMR ($CDCl_3$): 1.35 and 1.70 (each 2H, m, cyclopropane); 7.0-7.4 (4H, m, aromatics).

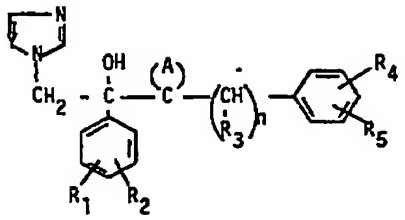
b) 1-(4-Fluorobenzoyl)-1-(4-fluorophenyl)cyclopropane
NMR ($CDCl_3$): 1.30 and 1.66 (each 2H, m, cyclopropane); 6.8-7.85 (8H, m, aromatics).

c) 1-(4-Fluorophenyl)-1-[1-(4-fluorophenyl)-1-hydroxy-2-phenylthio]ethyl-cyclopropane
NMR ($CDCl_3$): 0.48-0.85 (2H, m, cyclopropane); 1.32 (2H, m, cyclopropane); 3.07 (1H, s, −OH); 3.43 and 3.86 (each 1H, AB-q, J=13.1 Hz, $-SCH_2$); 6.8 - 7.3 (13H, m, aromatics).

d) 2-[1-(Fluorophenyl)cyclopropyl]-2-(4-fluorophenyl)oxirane
NMR ($CDCl_3$):
0.6-1.2 (4H, m, cyclopropane); 2.90 (1H, d, J=5.4 Hz); 3.08 (1H, d, J=5.4 Hz, $-CH_2O$); 6.8-7.3 (8H, m, aromatics).

CLAIMS

1. A compound of formula I



I

wherein

R_1 and R_2, independently, are hydrogen, halogen, nitro or unsubstituted or mono- or polyl-halogen substituted lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy or lower alkylthio or unsubstituted or substituted phenyl or phenoxy,

R_3 is hydrogen or lower alkyl,

R_4 and R_5, independently, are hydrogen or halogen,

Y is CH or N,

A is a C_{2-7} alkylene bridge and

n is 0 or 1.

2. A compound according to Claim 1 wherein

R_1 and R_2, independently, are hydrogen, halogen, nitro or optionally halogenated lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy or lower alkylthio or optionally substituted phenyl or phenoxy,

R_3 is hydrogen or alkyl,

R_4 is hydrogen or halogen,

R_5 is halogen,

Y is CH or N

A is a C_{2-7} alkylene bridge and

n is 0 or 1.

3. A compound according to Claim 1 wherein R_1, R_2, R_4 and R_5, independently, are hydrogen or halogen, R_3 is hydrogen.

4. A compound according to Claim 3 wherein R_1 and R_4 are hydrogen.

5. A compound according to Claim 4 wherein R_2 and R_5 independently are F or Cl.

6. A compound according to Claim 5 wherein R_2 and R_5 are in para-position.

7. A compound selected from

1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-chlorophenyl)cyclopropane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,3-imidazol-1-yl)ethyl]-1-(4-chlorophenyl)cyclopropane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-chlorophenyl)cyclopentane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,3-imidazol-1-yl)ethyl]-1-(4-chlorophenyl)cyclopentane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-chlorobenzyl)cyclopropane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,3-imidazol-1lyl)ethyl]-1-(4-chlorobenzyl)cyclopropane;
1-[1(4-chlorophenyl)-1-hydroxy-2-(1H-1,3-imidazol-1-yl)ethyl]-1-(4-chlorobenzyl)cyclopentane;
1-[1(4-chlorophenyl)-1-hydroxy-2(1H-1,2,4-triazol-1-yl)ethyl]-1-(2-fluorophenyl)cyclopropane;
1-[1(4-fluorophenyl-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-fluorophenyl)cyclopropane.

8. 1-[1-(4-chlorophenyl)-1-hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl]-1-(4-fluorophenyl)cyclopropane.

9. 1-[1-(4-chlorophenyl)-1-1hydroxy-2-(1H-1,2,4-triazol-1-yl)ethyl[-1-phenyl-cyclopropane.

10. A compound according to any one of Claims 1 to 9 in free base form.

11. A compound according to any one of Claims 1 to 9 in the form of an acid addition salt.

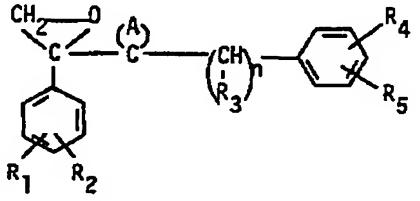
12. A compound according to any one of Claims 1 to 9 in the form of a physiologically-hydrolysable and -acceptable derivative.

13. A chemotherapeutical composition containing a compound according to any one of Claims 1 to 9 in free base form or in the form of a chemotherapeutically acceptable acid addition salt or physiologically-hydrolysable and -acceptable derivative thereof.

14. A compound according to any one of Claims 1 to 9 in free base form or in the form of a chemotherapeutically acceptable acid addition salt or physiologically-hydrolysable and -acceptable derivative thereof, for use as a chemotherapeutic agent.

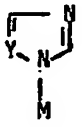
15. A compound according to any one of Claims 1 to 9 in free base form or in the form of a chemotherapeutically acceptable acid addition salt or physiologically-hydrolysable and -acceptable derivative thereof, for use as an anti-mycotic.

16. A process for preparing a compound according to Claim 1 acid addition and physiologically-hydrolysable and -acceptable derivatives thereof which comprises reacting a compound of formula II



II

with a compound of formula III



III

wherein

R_1 to R_5, Y, A and n are as defined above and

M is hydrogen, a metal, or a trialkylsilyl group,

and isolating the compound thus obtained in free base form or in the form of an acid addition salt or physiologically-hydrolysable and -acceptable derivative.

17. A compound of formula II according to Claim 16.

Printed in the UK for HMSO, D8818835, 3/85, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.